April 14, 2004

Uma Parasar
Senior Toxicologist
International Flavors & Fragrances
1040 Broad Street
Shrewsbury, NJ 07703

Dear Ms. Parasar:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl posted on the ChemRTK HPV Challenge Program Web site on December 15, 2003. I commend International Flavors & Fragrances for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that International Flavors & Fragrances advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
1,3,4,6,7,8-hexahydro-4,6,6,7,8,8,-hexamethylcyclopenta[g]-2-benzopyran (HHCB)

Summary of EPA Comments

The sponsor, International Flavors and Fragrances, submitted a test plan and robust summaries to EPA for 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8,-hexamethylcyclopenta[g]-2-benzopyran (HHCB, CAS No. 1222-05-5) dated October 31, 2003. EPA posted the submission on the ChemRTK HPV Challenge Website on December 15, 2003.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The submitted data are adequate for all endpoints for the purposes of the HPV Challenge Program.

2. Environmental Fate. The submitted data for photodegradation, biodegradation, and fugacity are adequate for the purposes of the HPV Challenge Program. The submitter needs to include the input values used in the fugacity model. The submitter also needs to present the "no-test" rationale in the robust summary for stability in water.

3. Health Effects. Data are adequate for acute and genetic toxicity endpoints for the purposes of the HPV Challenge Program. EPA reserves judgement on the adequacy of the repeated-dose, reproductive, and developmental toxicity data pending submission of additional information. The submitter needs to address several deficiencies in the robust summaries.

4. Ecological Effects. The submitted data are adequate for all endpoints for the purposes of the HPV Challenge Program. However, the submitter needs to provide information on the missing data elements in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the HHCB Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The submitted data are adequate for these endpoints for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The submitted data for photodegradation, biodegradation, and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. Strictly speaking, the benzyl ether moiety in the molecule is susceptible to hydrolysis. The submitter needs to discuss in the robust summary why it expects this reaction not to be environmentally significant.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Data are adequate for the acute and genetic toxicity endpoints for the purposes of the HPV Challenge Program. EPA reserves judgement on the adequacy of the repeated-dose, reproductive, and developmental toxicity data pending submission of additional information. The submitter needs to address numerous deficiencies in the robust summaries.

Given the reported acute oral LD50 values of greater than 3 g/kg, and the doses used in the developmental toxicity study (up to 500 mg/kg), it is not clear why the doses used in the repeated-dose and reproductive toxicity studies were so low. If the submitter provides missing elements from the developmental toxicity robust summary and an adequate justification for dose selection for the 13-week study with the information on evaluation of the reproductive organs in that study, it is likely that all of these endpoints will be considered adequate for the HPV Challenge Program.

Acute Toxicity. In the description of the first acute oral toxicity test plan, the submitter needs to include a reference–Moreno, 1975.

Repeated-Dose Toxicity. The repeated-dose oral toxicity study was conducted with the highest dose of 150 mg/kg/day, which is significantly lower than the OECD recommended limit dose of 1000 mg/kg/day and did not illicit any toxicity. The submitter needs to provide a rationale for the dose selection.

Reproductive Toxicity. Similar to the repeated-dose toxicity study, this study was also conducted with the highest dose (20 mg/kg/day) that was significantly lower than the OECD recommended limit dose of 1000 mg/kg/day with no adverse effects. The submitter needs to provide justification for selecting these dose levels.

Developmental Toxicity. The submitter needs to provide missing information in the robust summary to evaluate adequacy of the data.

Ecological Effects (fish, invertebrates, and algae).

The submitted data are adequate for all endpoints for the purposes of the HPV Challenge Program. However, the sponsor needs to provide information on the missing data elements in the robust summaries.

Specific Comments on the Robust Summaries

General. In general, the robust summaries, especially for the guideline studies, were missing several experimental details. The submitter should consult EPA guidance documents for the preparation of robust summaries (http://www.epa.gov/opptintr/chemrtk/guidocs.htm).

Environmental Fate

Fugacity. The submitter needs to include the input values used in the fugacity model.

Health Effects

Acute Toxicity. Missing information in the robust summaries includes the purity of the test substance and whether or not body weight measurements were taken and gross necropsy performed.

Repeated-Dose Toxicity. Missing information needed to evaluate the 13-week dietary assay in rats includes the parameters that were investigated (e.g., clinical signs, body weight changes, food consumption, organs weighed and histopathologically examined). Although the study was conducted under GLP and OECD TG 408, the dose level selection does not seem appropriate. An adequate justification for dose selection would be helpful.

Genetic Toxicity. A robust summary for a negative chromosomal aberration assay in Chinese hamster ovary cells was missing the number of metaphases examined per concentration, documentation on the use of positive controls, demonstration that an appropriate response was achieved by positive controls (if used), the statistical methods, and the criteria for positive results.

Reproductive Toxicity. The following information is missing: the numbers of animals tested, information on mating procedures, the exposure protocol (the summary states only females were used), the parameters examined, and the statistical methods. The summary erroneously stated that "a NOAEL was not established for this study" although no adverse effects were observed at any exposure level. The basis for dose level selection would be helpful because testing was done at doses at least 50 times lower than the OECD limit dose of 1000 mg/kg/day and no adverse effects were noted.

Developmental Toxicity. Missing information includes group size, the parameters that were examined for maternal and fetal toxicity, and incidence and/or percent change from control values and statistical significance of maternal and developmental toxicological effects. No information was provided to show the similarity of this guideline to OECD TG 414.

Ecological Effects

Fish.
Missing study details include the number of fish per concentration, percent mortality and toxicity by concentration, and water chemistry parameters including hardness, temperature, pH, and dissolved oxygen.

Invertebrates.
Missing study details include the number of daphnia per concentration, percent mortality by concentration, and water chemistry parameters including hardness, temperature, pH, and dissolved oxygen.

Algae.
Missing study details include test substance purity, number of replicates per concentration, growth inhibition by concentration, and test conditions (e.g., temperature and pH).

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.